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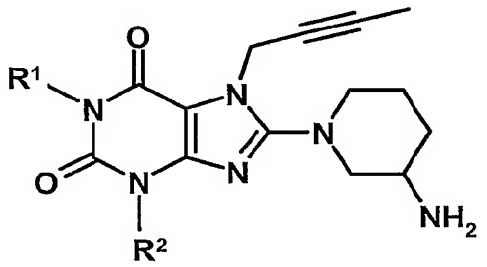
(54) 8-[3-AMINO-PIPERIDIN-1-YL]-XANTHINES, LEUR PRODUCTION ET LEUR UTILISATION COMME MEDICAMENT

(54) 8-[3-AMINO-PIPERIDIN-1-YL]-XANTHINES, THE PRODUCTION THEREOF, AND THE USE OF THE SAME AS MEDICAMENTS

(57)

The invention relates to substituted xanthines of general formula (I) wherein R1 and R2 have the designations cited in patent claims 1 to 3. The invention also relates to the tautomers, stereoisomers, mixtures and salts of said xanthines, exhibiting valuable pharmacological properties, especially an inhibiting effect on the activity of the enzyme dipeptidylpeptidase-IV (DPP- IV).



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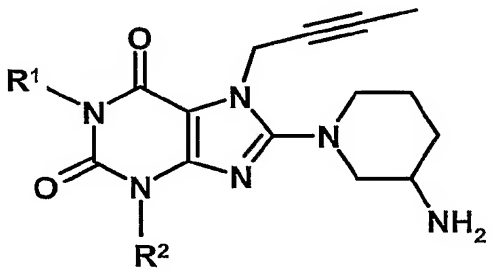
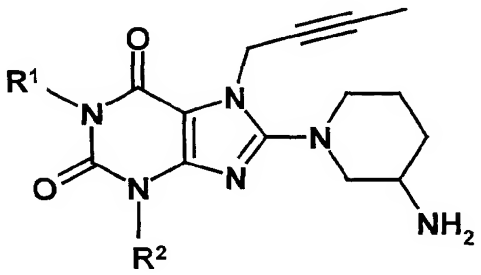


(I)

(57) Abrégé/Abstract:
The invention relates to substituted xanthines of general formula (I) wherein R^1 and R^2 have the designations cited in patent claims 1 to 3. The invention also relates to the tautomers, stereoisomers, mixtures and salts of said xanthines, exhibiting valuable pharmacological properties, especially an inhibiting effect on the activity of the enzyme dipeptidylpeptidase-IV (DPP-IV).

Abstract

The present invention relates to substituted xanthines of general formula



(I),

wherein R^1 and R^2 are defined as in claims 1 to 3, the tautomers, the stereoisomers, the mixtures thereof and the salts thereof, which have valuable pharmacological properties, particularly an inhibiting effect on the activity of the enzyme dipeptidylpeptidase-IV (DPP-IV).

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8-[3-Amino-piperidin-1-yl]-xanthines, their preparation and their use as pharmaceutical composition

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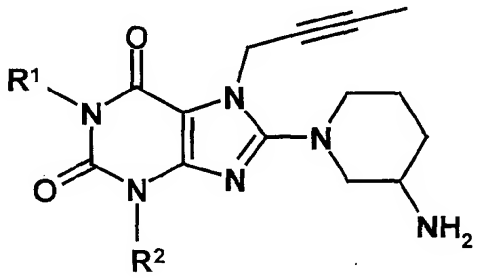
The present invention relates to new substituted xanthines of general formula



(I),

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases which have valuable pharmacological properties, particularly an inhibiting effect on the activity of the enzyme dipeptidylpeptidase-IV (DPP-IV), the preparation thereof, the use thereof for preventing or treating illnesses or conditions connected with an increased DPP-IV activity or capable of being prevented or alleviated by reducing the DPP-IV activity, particularly type I or type II diabetes mellitus, the pharmaceutical compositions containing a compound of general formula (I) or a physiologically acceptable salt thereof and processes for the preparation thereof.

Structurally similar compounds are described for example in WO 02/068420.

In the above formula I

R^1 denotes a benzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-(trifluoromethyl)-benzyl, 3-(trifluoromethyl)-benzyl or 4-(trifluoromethyl)-benzyl group,

a 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-(difluoromethoxy)-benzyl, 3-(difluoromethoxy)-benzyl, 4-(difluoromethoxy)-benzyl, 2-(trifluoromethoxy)-benzyl, 3-(trifluoromethoxy)-benzyl or 4-(trifluoromethoxy)-benzyl group,

a 2-cyanobenzyl, 3-cyanobenzyl or 4-cyanobenzyl group,

a 2-cyano-3-methoxy-benzyl, 2-cyano-4-methoxy-benzyl, 2-cyano-5-methoxy-benzyl, 2-cyano-4-fluoro-benzyl, 2-cyano-5-fluoro-benzyl or 2-cyano-6-fluoro-benzyl group,

a 2-oxo-2-phenyl-ethyl or 2-(3-methoxy-phenyl)-2-oxo-ethyl group,

a 2-(3-methyl-2-oxo-2,3-dihydro-benzoxazol-4-yl)-2-oxo-ethyl group,

a (pyridin-2-yl)methyl, (3-cyanopyridin-2-yl)methyl, (6-cyanopyridin-2-yl)methyl, (5-cyano-pyridin-2-yl)methyl, (4-cyano-pyridin-2-yl)methyl, (4-cyano-pyridin-3-yl)methyl, (3-cyano-pyridin-4-yl)methyl, (2-cyano-pyridin-3-yl)methyl, (2-cyano-pyridin-4-yl)methyl, (5-cyano-pyridin-3-yl)methyl or (6-cyano-pyridin-3-yl)methyl group,

a (3-cyano-quinolin-2-yl)methyl group,

a (1-cyano-isoquinolin-3-yl)methyl or (4-cyano-isoquinolin-1-yl)methyl group,

a (4-methyl-quinazolin-2-yl)methyl group,

a (quinoxalin-6-yl)methyl or (2,3-dimethyl-quinoxalin-6-yl)methyl group, or

a ([1,5]naphthyridin-2-yl)methyl group and

R^2 denotes a cyclopropyl or phenyl group,

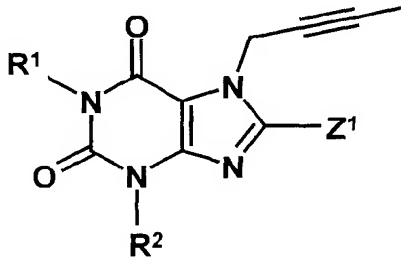
the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

In a second aspect the invention relates to compounds of general formula (I) wherein R^1 is as hereinbefore defined and R^2 denotes a cyclopropyl group, the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

In a third aspect the invention relates to compounds of general formula (I) wherein R^1 is as hereinbefore defined and R^2 denotes a phenyl group, the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

According to the invention the compounds of general formula I are obtained by methods known *per se*, for example by the following methods:

a) reacting a compound of general formula



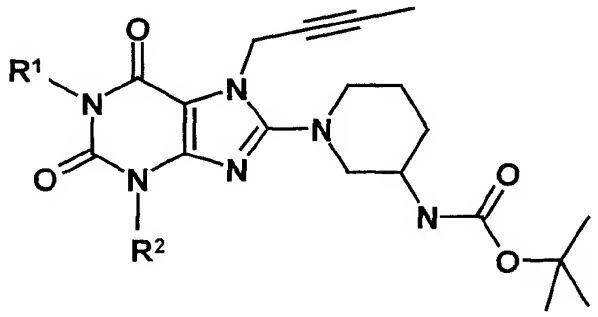
(II),

wherein
R^1 and R^2 are as hereinbefore defined and
Z^1 denotes a leaving group such as a halogen atom, a substituted hydroxy, mercapto, sulphinyl, sulphonyl or sulphonyloxy group such as a chlorine or bromine atom, a methanesulphonyl or methanesulphonyloxy group, with 3-aminopiperidine, the enantiomers thereof or the salts thereof.

The reaction is expediently carried out in a solvent such as isopropanol, butanol, tetrahydrofuran, dioxane, dimethylformamide, dimethylsulphoxide, ethyleneglycolmonomethylether, ethyleneglycoldiethylether or sulpholane, optionally in the presence of an inorganic or tertiary organic base, e.g. sodium carbonate, potassium carbonate or potassium hydroxide, a tertiary organic base, e.g. triethylamine, or in the presence of N-ethyl-diisopropylamine (Hünig base), while these organic bases

may simultaneously also serve as solvent, and optionally in the presence of a reaction accelerator such as an alkali metal halide or a palladium-based catalyst at temperatures between -20 and 180°C, but preferably at temperatures between -10 and 120°C. The reaction may however also be carried out without a solvent or in an excess of the 3-aminopiperidine.

b) deprotecting a compound of general formula



(III),

R^1 and R^2 are as hereinbefore defined.

The tert.-butyloxycarbonyl group is preferably cleaved by treatment with an acid such as trifluoroacetic acid or hydrochloric acid or by treatment with bromotrimethylsilane or iodotrimethylsilane, optionally using a solvent such as methylene chloride, ethyl acetate, dioxane, methanol, isopropanol or diethyl ether at temperatures between 0 and 80°C.

In the reactions described hereinbefore, any reactive groups present such as amino, alkylamino or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.

For example, protecting groups for an amino, alkylamino or imino group may be a formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group.

Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide or aprotically, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example, hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 100°C, but preferably at ambient temperatures between 20 and 60°C, and at a hydrogen pressure of 1 to 7 bar, but preferably from 3 to 5 bar. However, a 2,4-dimethoxybenzyl group is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert. butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with iodotrimethylsilane, optionally using a solvent such as methylene chloride, dioxane, methanol or diethyl ether.

A trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid at temperatures between 50 and 120°C or by treating with sodium hydroxide solution, optionally in the presence of a solvent such as tetrahydrofuran, at temperatures between 0 and 50°C.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between 20 and 50°C.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the *cis/trans* mixtures obtained may be separated by chromatography into their *cis* and *trans* isomers, the compounds of general formula I obtained which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical enantiomers and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be, for example, (+) or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)- or (-)-menthyloxycarbonyl.

Furthermore, the compounds of formula I obtained may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts

with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, methanesulphonic acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

The compounds of general formulae II and III used as starting compounds are either known from the literature or may be prepared by methods known from the literature (see Examples I to VII).

As already mentioned hereinbefore, the compounds of general formula I according to the invention and the physiologically acceptable salts thereof have valuable pharmacological properties, particularly an inhibiting effect on the enzyme DPP-IV.

The biological properties of the new compounds were investigated as follows:

The ability of the substances and their corresponding salts to inhibit the DPP-IV activity can be demonstrated in an experiment in which an extract of the human colon carcinoma cell line Caco-2 is used as the DPP IV source. The differentiation of the cells in order to induce the DPP-IV expression was carried out in accordance with the description by Reiher *et al.* in an article entitled "Increased expression of intestinal cell line Caco-2" , which appeared in Proc. Natl. Acad. Sci. Vol. 90, pp. 5757-5761 (1993). The cell extract was obtained from cells solubilised in a buffer (10mM Tris HCl, 0.15 M NaCl, 0.04 t.i.u. aprotinin, 0.5% Nonidet-P40, pH 8.0) by centrifugation at 35,000 g for 30 minutes at 4°C (to remove cell debris).

The DPP-IV assay was carried out as follows:

50 µl of substrate solution (AFC; AFC is amido-4-trifluoromethylcoumarin), final concentration 100 µM, were placed in black microtitre plates. 20 µl of assay buffer (final concentrations 50 mM Tris HCl pH 7.8, 50 mM NaCl, 1 % DMSO) was pipetted in. The reaction was started by the addition of 30 µl of solubilised Caco-2 protein (final concentration 0.14 µg of protein per well). The test substances under

investigation were typically added prediluted to 20 µl, while the volume of assay buffer was then reduced accordingly. The reaction was carried out at ambient temperature, the incubation period was 60 minutes. Then the fluorescence was measured in a Victor 1420 Multilabel Counter, with the excitation wavelength at 405 nm and the emission wavelength at 535 nm. Dummy values (corresponding to 0 % activity) were obtained in mixtures with no Caco-2 protein (volume replaced by assay buffer), control values (corresponding to 100 % activity) were obtained in mixtures without any added substance. The potency of the test substances in question, expressed as IC_{50} values, were calculated from dosage/activity curves consisting of 11 measured points in each case. The following results were obtained:

Compound (Example no.)	DPP IV inhibition IC_{50} [nM]
1	3.6
1(1)	2.7
1(8)	4.9
1(10)	8.1
1(13)	4.0
1(15)	1.5

The compounds prepared according to the invention are well tolerated as no toxic side effects could be detected in rats after the oral administration of 10 mg/kg of the compound of Example 1(8), for example.

In view of their ability to inhibit DPP-IV activity, the compounds of general formula I according to the invention and the corresponding pharmaceutically acceptable salts thereof are suitable for influencing any conditions or diseases which can be affected by the inhibition of the DPP-IV activity. It is therefore to be expected that the compounds according to the invention will be suitable for the prevention or treatment of diseases or conditions such as type I and type II diabetes mellitus, prediabetes, reduced glucose tolerance or changes in the fasting blood sugar, diabetic complications (e.g. retinopathy, nephropathy or neuropathies), metabolic acidosis or

ketosis, reactive hypoglycaemia, insulin resistance, metabolic syndrome, dyslipidaemias of various origins, arthritis, atherosclerosis and related diseases, obesity, allograft transplantation and osteoporosis caused by calcitonin. In addition, these substances are suitable for preventing B-cell degeneration such as e.g. apoptosis or necrosis of pancreatic B-cells. The substances are also suitable for improving or restoring the function of pancreatic cells and additionally increasing the size and number of pancreatic B-cells. Additionally, on the basis of the role of the glucagon-like peptides such as e.g. GLP-1 and GLP-2 and their link with DPP-IV inhibition, it is expected that the compounds according to the invention will be suitable for achieving, *inter alia*, a sedative or tranquillising effect, as well as having a favourable effect on catabolic states after operations or hormonal stress responses or possibly reducing mortality and morbidity after myocardial infarct. Moreover, they are suitable for treating any conditions connected with the effects mentioned above and mediated by GLP-1 or GLP-2. The compounds according to the invention may also be used as diuretics or antihypertensives and are suitable for preventing and treating acute kidney failure. The compounds according to the invention may also be used to treat inflammatory complaints of the respiratory tract. They are also suitable for preventing and treating chronic inflammatory bowel diseases such as e.g. irritable bowel syndrome (IBS), Crohn's disease or ulcerative colitis and also pancreatitis. It is also expected that they can be used for all kinds of injury or damage to the gastrointestinal tract such as may occur in colitis and enteritis, for example. Moreover, it is expected that DPP-IV inhibitors and hence the compounds according to the invention can be used to treat infertility or to improve fertility in humans or mammals, particularly if the infertility is connected with insulin resistance or with polycystic ovary syndrome. On the other hand these substances are suitable for influencing sperm motility and are thus suitable for use as male contraceptives. In addition, the substances are suitable for treating growth hormone deficiencies connected with restricted growth, and may reasonably be used for all indications for which growth hormone may be used. The compounds according to the invention are also suitable, on the basis of their inhibitory effect on DPP-IV, for treating various autoimmune diseases such as e.g. rheumatoid arthritis, multiple sclerosis, thyroiditis and Basedow's disease, etc. They may also be used to treat viral diseases and also,

for example, in HIV infections, for stimulating blood production, in benign prostatic hyperplasia, gingivitis, as well as for the treatment of neuronal defects and neurodegenerative diseases such as Alzheimer's disease, for example. The compounds described may also be used for the treatment of tumours, particularly for modifying tumour invasion and also metastasisation; examples here are their use in treating T-cell lymphomas, acute lymphoblastic leukaemia, cell-based pancreatic carcinomas, basal cell carcinomas or breast cancers. Other indications are stroke, ischaemia of various origins, Parkinson's disease and migraine. In addition, further indications include follicular and epidermal hyperkeratoses, increased keratinocyte proliferation, psoriasis, encephalomyelitis, glomerulonephritis, lipodystrophies, as well as psychosomatic, depressive and neuropsychiatric diseases of all kinds.

The compounds according to the invention may also be used in conjunction with other active substances. Suitable therapeutic agents for such combinations include for example antidiabetic agents such as metformin, sulphonylureas (e.g. glibenclamid, tolbutamide, glimepiride), nateglinide, repaglinide, thiazolidinediones (e.g. rosiglitazone, pioglitazone), PPAR-gamma agonists (e.g. GI 262570) and antagonists, PPAR-gamma/alpha modulators (e.g. KRP 297), PPAR-gamma/alpha/delta modulators, AMPK activators, ACC1 and ACC2 inhibitors, DGAT inhibitors, SMT3 receptor agonists, 11ß-HSD inhibitors, FGF19 agonists or mimetics, alpha-glucosidase inhibitors (e.g. acarbose, voglibose), other DPPIV inhibitors, alpha2 antagonists, insulin and insulin analogues, GLP-1 and GLP-1 analogues (e.g. exendin-4) or amylin. Also, combinations with SGLT2 inhibitors such as T-1095 or KGT-1251 (869682), inhibitors of protein tyrosine phosphatase 1, substances which influence deregulated glucose production in the liver, such as e.g. inhibitors of glucose-6-phosphatase, or fructose-1,6-bisphosphatase, glycogen phosphorylase, glucagon receptor antagonists and inhibitors of phosphoenol pyruvate carboxykinase, glycogen synthase kinase or pyruvate dehydrokinase, lipid lowering agents, such as HMG-CoA-reductase inhibitors (e.g. simvastatin, atorvastatin), fibrates (e.g. bezafibrate, fenofibrate), nicotinic acid and its derivatives, PPAR-alpha agonists, PPAR-delta agonists, ACAT inhibitors (e.g. avasimibe) or cholesterol absorption inhibitors such as for example ezetimibe, bile acid-binding substances

such as for example cholestyramine, inhibitors of ileac bile acid transport, HDL-raising compounds such as for example inhibitors of CETP or regulators of ABC1 or LXRalpha antagonists, LXRbeta agonists or LXRalpha/beta regulators or active substances for the treatment of obesity, such as e.g. sibutramine or tetrahydrolipostatin, dexfenfluramine, axokine, antagonists of the cannabinoid1 receptor, MCH-1 receptor antagonists, MC4 receptor agonists, NPY5 or NPY2 antagonists or $ß_3$-agonists such as SB-418790 or AD-9677 as well as agonists of the 5HT2c receptor.

It is also possible to combine the compounds with drugs for treating high blood pressure such as e.g. All antagonists or ACE inhibitors, diuretics, ß-blockers, Ca-antagonists, etc., or combinations thereof.

The dosage required to achieve such an effect is expediently, by intravenous route, 1 to 100 mg, preferably 1 to 30 mg, and by oral route 1 to 1000 mg, preferably 1 to 100 mg, in each case 1 to 4 times a day. For this purpose, the compounds of formula I prepared according to the invention, optionally combined with other active substances, may be incorporated together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

The Examples that follow are intended to illustrate the invention:

Preparation of the starting compounds

Example I

1-[2-(3-methyl-2-oxo-2,3-dihydro-benzoxazol-4-yl)-2-oxo-ethyl]-3-cyclopropyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

A mixture of 250 mg of 3-cyclopropyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine, 175 mg of 4-(2-bromo-acetyl)-3-methyl-3*H*-benzoxazol-2-one and 300 mg potassium carbonate in 3 ml N,N-dimethylformamide is stirred for one hour at 75°C, then another 60 mg of 4-(2-bromo-acetyl)-3-methyl-3*H*-benzoxazol-2-one are added. After a further 1.5 hours the reaction is complete and the reaction mixture is combined with ice water. The precipitate that crystallises out is suction filtered, washed with water and dissolved in methylene chloride. The solution is dried over magnesium sulphate and evaporated down. The crude product is brought to crystallisation with diethyl ether, suction filtered and dried.

Yield: 310 mg (87 % of theory)

R_f value: 0.56 (silica gel, methylene chloride/methanol = 95:5)

Mass spectrum (ESI^+): m/z = 632 $[M+H]^+$

The following compounds are obtained analogously to Example I:

(1) 1-[(4-methyl-quinazolin-2-yl)methyl]-3-cyclopropyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

R_f value: 0.40 (silica gel, ethyl acetate)

Mass spectrum (ESI^+): m/z = 599 $[M+H]^+$

(2) 1-[2-(3-methoxy-phenyl)-2-oxo-ethyl]-3-cyclopropyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

R_f value: 0.60 (silica gel, methylene chloride/ethyl acetate = 1:1)

Mass spectrum (ESI^+): m/z = 591 $[M+H]^+$

(3) 1-[(4-cyano-isoquinolin-1-yl)methyl]-3-cyclopropyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

R_f value: 0.65 (silica gel, ethyl acetate)
Mass spectrum (ESI^+): m/z = 609 $[M+H]^+$

(4) 1-[(1-cyano-isoquinolin-3-yl)methyl]-3-cyclopropyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.59 (silica gel, ethyl acetate/petroleum ether = 4:1)
Mass spectrum (ESI^+): m/z = 609 $[M+H]^+$

(5) 1-[([1,5]naphthyridin-2-yl)methyl]-3-cyclopropyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.48 (silica gel, ethyl acetate/methanol = 95:5)
Mass spectrum (ESI^+): m/z = 585 $[M+H]^+$

(6) 1-[(2,3-dimethyl-quinoxalin-6-yl)methyl]-3-cyclopropyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.38 (silica gel, ethyl acetate)
Mass spectrum (ESI^+): m/z = 613 $[M+H]^+$

(7) 1-(2-oxo-2-phenyl-ethyl)-3-phenyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonyl-amino)-piperidin-1-yl]-xanthine
R_f value: 0.65 (silica gel, methylene chloride/ethyl acetate = 7:3)
Mass spectrum (ESI^+): m/z = 597 $[M+H]^+$

(8) 1-[(4-methyl-quinazolin-2-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.67 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)
Mass spectrum (ESI^+): m/z = 635 $[M+H]^+$

(9) 1-[2-(3-methyl-2-oxo-2,3-dihydro-benzoxazol-4-yl)-2-oxo-ethyl]-3-phenyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine
R_f value: 0.52 (silica gel, methylene chloride/methanol = 95:5)

Mass spectrum (ESI$^+$): m/z = 668 $[M+H]^+$

(10) 1-[2-(3-methoxy-phenyl)-2-oxo-ethyl]-3-phenyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

R_f value: 0.85 (silica gel, methylene chloride/ethyl acetate = 1:1)

Mass spectrum (ESI$^+$): m/z = 627 $[M+H]^+$

(11) 1-[(4-cyano-isoquinolin-1-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

R_f value: 0.85 (silica gel, ethyl acetate)

Mass spectrum (ESI$^+$): m/z = 645 $[M+H]^+$

(12) 1-[(1-cyano-isoquinolin-3-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

R_f value: 0.74 (silica gel, ethyl acetate/petroleum ether = 4:1)

Mass spectrum (ESI$^+$): m/z = 645 $[M+H]^+$

(13) 1-[([1,5]naphthyridin-2-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

R_f value: 0.62(silica gel, ethyl acetate/methanol = 95:5)

Mass spectrum (ESI$^+$): m/z = 621 $[M+H]^+$

(14) 1-[(2,3-dimethyl-quinoxalin-6-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

R_f value: 0.59 (silica gel, ethyl acetate)

Mass spectrum (ESI$^+$): m/z = 649 $[M+H]^+$

(15) 1-(2-cyano-benzyl)-3-phenyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonyl-amino)-piperidin-1-yl]-xanthine

R_f value: 0.90 (silica gel, methylene chloride/ethyl acetate = 1:1)

Mass spectrum (ESI$^+$): m/z = 594 $[M+H]^+$

(17) 1-(2-cyano-benzyl)-3-cyclopropyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxy-carbonylamino)-piperidin-1-yl]-xanthine

R_f value: 0.70 (silica gel, methylene chloride/ethyl acetate = 1:1)

Mass spectrum (ESI^+): m/z = 558 $[M+H]^+$

Example II

3-Cyclopropyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

Prepared by reacting 3-cyclopropyl-7-(2-butyn-1-yl)-8-bromo-xanthine with (*R*)-3-tert.-butyloxycarbonylamino-piperidine in the presence of potassium carbonate in dimethylsulphoxide at 80°C.

R_f value: 0.35 (reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 50:50:1)

Mass spectrum (ESI^+): m/z = 443 $[M+H]^+$

The following compound is obtained analogously to Example II:

(1) 3-phenyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine

R_f value: 0.25 (reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 50:50:1)

Mass spectrum (ESI^+): m/z = 479 $[M+H]^+$

Example III

3-Cyclopropyl-7-(2-butyn-1-yl)-8-bromo-xanthine

Prepared by reacting 3-cyclopropyl-8-bromo-xanthine with 1-bromo-2-butyne in the presence of diisopropylethylamine in N,N-dimethylformamide at ambient temperature.

R_f value: 0. 45 (reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 50:50:1)

Mass spectrum (ESI^+): m/z = 323, 325 $[M+H]^+$

The following compound is obtained analogously to Example III:

(1) 3-phenyl-7-(2-butyn-1-yl)-8-bromo-xanthine
R_f value: 0.41 (reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 50:50:1)
Mass spectrum (ESI^+): m/z = 359, 361 $[M+H]^+$

Example IV

3-Cyclopropyl-8-bromo-xanthine

Prepared by reacting 3-cyclopropyl-xanthine with bromine in the presence of potassium carbonate in acetonitrile at 60°C.
R_f value: 0.65 (reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 50:50:1)
Mass spectrum (ESI^+): m/z = 271, 273 $[M+H]^+$

The following compound is obtained analogously to Example IV:

(1) 3-phenyl-8-bromo-xanthine
R_f value: 0.54 (reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 50:50:1)
Mass spectrum (ESI^+): m/z = 307, 309 $[M+H]^+$

Example V

4-(2-Bromo-acetyl)-3-methyl-3*H*-benzoxazol-2-one

Prepared by bromination of 4-acetyl-3-methyl-3*H*-benzoxazol-2-on in methylene chloride at ambient temperature.
R_f value: 0.50 (silica gel, petroleum ether/ethyl acetate = 2:1)
Mass spectrum (ESI^+): m/z = 270, 272 $[M+H]^+$

Example VI

4-Acetyl-3-methyl-3*H*-benzoxazol-2-one

Prepared by reacting 4-acetyl-3*H*-benzoxazol-2-one with methyl iodide in the presence of potassium-tert.-butoxide in N,N-dimethylformamide at ambient temperature.

R_f value: 0.40 (silica gel, petroleum ether/ethyl acetate = 2:1)

Mass spectrum (ESI^+): m/z = 192 $[M+H]^+$

Example VII

1-Bromomethyl-4-cyano-isoquinoline

Prepared by treating 1-methyl-4-cyano-isoquinoline with N-bromo-succinimide in the presence of azobisisobutyronitrile in carbon tetrachloride at reflux temperature.

R_f value: 0.58 (silica gel, methylene chloride)

Mass spectrum (ESI^+): m/z = 247, 249 $[M+H]^+$

The following compounds are obtained analogously to Example VII:

(1) 3-bromomethyl-1-cyano-isoquinoline

R_f value: 0.61 (silica gel, methylene chloride)

Mass spectrum (ESI^+): m/z = 247, 249 $[M+H]^+$

(2) 2-bromomethyl-[1,5]naphthyridine

R_f value: 0.60 (aluminium oxide, methylene chloride)

Mass spectrum (ESI^+): m/z = 223, 225 $[M+H]^+$

Preparation of the end compounds

Example 1

1-[2-(3-Methyl-2-oxo-2,3-dihydro-benzoxazol-4-yl)-2-oxo-ethyl]-3-cyclopropyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine

1.5 ml isopropanolic hydrochloric acid (5-6 M) are added to 300 mg 1-[2-(3-methyl-2-oxo-2,3-dihydro-benzoxazol-4-yl)-2-oxo-ethyl]-3-cyclopropyl-7-(2-butyn-1-yl)-8-[(*R*)-3-(tert.-butyloxycarbonylamino)-piperidin-1-yl]-xanthine in 5 ml methylene chloride and the reaction mixture is stirred for 5.5 hours at ambient temperature.
Then the mixture is made alkaline with 8 ml 1N sodium hydroxide solution and extracted with a mixture of methylene chloride and methanol. The combined organic phases are washed with saturated sodium chloride solution, dried over magnesium sulphate and evaporated down. The flask residue is chromatographed through a silica gel column with methylene chloride/methanol/methanolic ammonia solution (98:2:0 to 94:5:1) as eluant. The crude product is brought to crystallisation with diethyl ether, suction filtered, washed and dried.
Yield: 140 mg (55 % of theory)
melting point: 168-171°C
Mass spectrum (ESI^+): m/z = 532 $[M+H]^+$

The following compounds are obtained analogously to Example 1:

(1) 1-[(4-methyl-quinazolin-2-yl)methyl]-3-cyclopropyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine
(BOC cleaving carried out with trifluoroacetic acid)
R_f value: 0. 55 (reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/trifluoroacetic acid = 50:50:1)
Mass spectrum (ESI^+): m/z = 499 $[M+H]^+$

(2) 1-[2-(3-methoxy-phenyl)-2-oxo-ethyl]-3-cyclopropyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine
(BOC cleaving carried out with trifluoroacetic acid)

R_f value: 0. 35 (reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 50:50:1)
Mass spectrum (ESI^+): m/z = 491 $[M+H]^+$

(3) 1-[(4-cyano-isoquinolin-1-yl)methyl]-3-cyclopropyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine
R_f value: 0.38 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)
Mass spectrum (ESI^+): m/z = 509 $[M+H]^+$

(4) 1-[(1-cyano-isoquinolin-3-yl)methyl]-3-cyclopropyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine
R_f value: 0.32 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)
Mass spectrum (ESI^+): m/z = 509 $[M+H]^+$

(5) 1-[([1,5]naphthyridin-2-yl)methyl]-3-cyclopropyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine
R_f value: 0.39 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)
Mass spectrum (ESI^+): m/z = 485 $[M+H]^+$

(6) 1-[(2,3-dimethyl-quinoxalin-6-yl)methyl]-3-cyclopropyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine
R_f value: 0.50 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)
Mass spectrum (ESI^+): m/z = 513 $[M+H]^+$

(7) 1-(2-oxo-2-phenyl-ethyl)-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine
R_f value: 0.40 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)

Mass spectrum (ESI$^+$): m/z = 497 $[M+H]^+$

(8) 1-[(4-methyl-quinazolin-2-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

R_f value: 0.32 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)

Mass spectrum (ESI$^+$): m/z = 535 $[M+H]^+$

(9) 1-[2-(3-methyl-2-oxo-2,3-dihydro-benzoxazol-4-yl)-2-oxo-ethyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

R_f value: 0.53 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)

Mass spectrum (ESI$^+$): m/z = 568 $[M+H]^+$

(10) 1-[2-(3-methoxy-phenyl)-2-oxo-ethyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

R_f value: 0. 30 (reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/trifluoroacetic acid = 50:50:1)

Mass spectrum (ESI$^+$): m/z = 527 $[M+H]^+$

(11) 1-[(4-cyano-isoquinolin-1-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

R_f value: 0.45 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)

Mass spectrum (ESI$^+$): m/z = 545 $[M+H]^+$

(12) 1-[(1-cyano-isoquinolin-3-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

R_f value: 0.37 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)

Mass spectrum (ESI$^+$): m/z = 545 $[M+H]^+$

(13) 1-[([1,5]naphthyridin-2-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

R_f value: 0.42 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)

Mass spectrum (ESI^+): m/z = 521 $[M+H]^+$

(14) 1-[(2,3-dimethyl-quinoxalin-6-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

R_f value: 0.51 (silica gel, methylene chloride/methanol/conc. aqueous ammonia = 90:10:1)

Mass spectrum (ESI^+): m/z = 549 $[M+H]^+$

(15) 1-(2-cyano-benzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(BOC cleaving carried out with trifluoroacetic acid)

R_f value: 0. 45 (reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 50:50:1)

Mass spectrum (ESI^+): m/z = 494 $[M+H]^+$

(16) 1-(2-cyano-benzyl)-3-cyclopropyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

R_f value: 0. 45 (reversed phase ready-made TLC plate (E. Merck), acetonitrile/water/ trifluoroacetic acid = 50:50:1)

Mass spectrum (ESI^+): m/z = 458 $[M+H]^+$

The following compounds may also be obtained analogously to the foregoing Examples and other methods known from the literature:

(1) 1-(2-cyano-4-fluoro-benzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(2) 1-(2-cyano-5-fluoro-benzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(3) 1-(2-cyano-6-fluoro-benzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(4) 1-(3-cyanobenzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(5) 1-(4-cyanobenzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(6) 1-benzyl-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(7) 1-[(pyridin-2-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(8) 1-(2-chlorobenzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(9) 1-(2-fluoro-benzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(10) 1-[(3-cyano-pyridin-2-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(11) 1-[(6-cyano-pyridin-2-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(12) 1-[(5-cyano-pyridin-2-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(13) 1-[(4-cyano-pyridin-2-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(14) 1-[(4-cyano-pyridin-3-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(15) 1-[(3-cyano-pyridin-4-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(16) 1-[(2-cyano-pyridin-3-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(17) 1-[(2-cyano-pyridin-4-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(18) 1-[(5-cyano-pyridin-3-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(19) 1-[(6-cyano-pyridin-3-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(20) 1-(2-cyano-4-methoxy-benzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(21) 1-(2-cyano-5-methoxy-benzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(22) 1-[(3-cyano-quinolin-2-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(23) 1-(2-methoxy-benzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(24) 1-(2-trifluoromethyl-benzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(25) 1-[(quinoxalin-6-yl)methyl]-3-phenyl-7-(2-butyn-1-yl)-8-((*R*)-3-amino-piperidin-1-yl)-xanthine

(26) 1-(3-fluoro-benzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine

(27) 1-(4-fluoro-benzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine

(28) 1-(3-chlorobenzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine

(29) 1-(4-chlorobenzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine

(30) 1-[3-(trifluoromethyl)-benzyl]-3-phenyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine

(31) 1-[4-(trifluoromethyl)-benzyl]-3-phenyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine

(32) 1-(3-methoxy-benzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine

(33) 1-(4-methoxy-benzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine

(34) 1-[2-(difluoromethoxy)-benzyl]-3-phenyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine

(35) 1-[3-(difluoromethoxy)-benzyl]-3-phenyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine

(36) 1-[4-(difluoromethoxy)-benzyl]-3-phenyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine

(37) 1-[2-(trifluoromethoxy)-benzyl]-3-phenyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine

(38) 1-[3-(trifluoromethoxy)-benzyl]-3-phenyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine

(39) 1-[4-(trifluoromethoxy)-benzyl]-3-phenyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine

(40) 1-(2-cyano-3-methoxy-benzyl)-3-phenyl-7-(2-butyn-1-yl)-8-((R)-3-amino-piperidin-1-yl)-xanthine

Example 2

Coated tablets containing 75 mg of active substance

1 tablet core contains:

active substance	75.0 mg
calcium phosphate	93.0 mg
corn starch	35.5 mg
polyvinylpyrrolidone	10.0 mg
hydroxypropylmethylcellulose	15.0 mg
magnesium stearate	1.5 mg
	230.0 mg

Preparation:

The active substance is mixed with calcium phosphate, corn starch, polyvinylpyrrolidone, hydroxypropylmethylcellulose and half the specified amount of magnesium stearate. Blanks about 13 mm in diameter are produced in a tablet-making machine and these are then rubbed through a screen with a mesh size of 1.5 mm using a suitable machine and mixed with the rest of the magnesium stearate. This granulate is compressed in a tablet-making machine to form tablets of the desired shape.

weight of core: 230 mg

die: 9 mm, convex

The tablet cores thus produced are coated with a film consisting essentially of hydroxypropylmethylcellulose. The finished film-coated tablets are polished with beeswax.

Weight of coated tablet: 245 mg.

Example 3

Tablets containing 100 mg of active substance

Composition:

1 tablet contains:

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	2.0 mg
	220.0 mg

Method of Preparation:

The active substance, lactose and starch are mixed together and uniformly moistened with an aqueous solution of the polyvinylpyrrolidone. After the moist composition has been screened (2.0 mm mesh size) and dried in a rack-type drier at 50°C it is screened again (1.5 mm mesh size) and the lubricant is added. The finished mixture is compressed to form tablets.

Weight of tablet: 220 mg

Diameter: 10 mm, biplanar, facetted on both sides and notched on one side.

Example 4

Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

active substance	150.0 mg
powdered lactose	89.0 mg
corn starch	40.0 mg
colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	1.0 mg
	300.0 mg

Preparation:

The active substance mixed with lactose, corn starch and silica is moistened with a 20% aqueous polyvinylpyrrolidone solution and passed through a screen with a mesh size of 1.5 mm.

The granules, dried at 45°C, are passed through the same screen again and mixed with the specified amount of magnesium stearate. Tablets are pressed from the mixture.

Weight of tablet: 300 mg

die: 10 mm, flat

Example 5

Hard gelatine capsules containing 150 mg of active substance

1 capsule contains:

active substance		150.0 mg
corn starch (dried)	approx.	180.0 mg
lactose (powdered)	approx.	87.0 mg
magnesium stearate		3.0 mg
	approx.	420.0 mg

Preparation:

The active substance is mixed with the excipients, passed through a screen with a mesh size of 0.75 mm and homogeneously mixed using a suitable apparatus. The finished mixture is packed into size 1 hard gelatine capsules.

Capsule filling: approx. 320 mg

Capsule shell: size 1 hard gelatine capsule.

Example 6

Suppositories containing 150 mg of active substance

1 suppository contains:

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg
polyoxyethylene sorbitan monostearate	840.0 mg
	2,000.0 mg

Preparation:

After the suppository mass has been melted the active substance is homogeneously distributed therein and the melt is poured into chilled moulds.

Example 7

Suspension containing 50 mg of active substance

100 ml of suspension contain:

active substance		1.00 g
carboxymethylcellulose-Na-salt		0.10 g
methyl p-hydroxybenzoate		0.05 g
propyl p-hydroxybenzoate		0.01 g
glucose		10.00 g
glycerol		5.00 g
70% sorbitol solution		20.00 g
flavouring		0.30 g
dist. water	ad	100 ml

Preparation:

The distilled water is heated to 70°C. The methyl and propyl p-hydroxybenzoates together with the glycerol and sodium salt of carboxymethylcellulose are dissolved therein with stirring. The solution is cooled to ambient temperature and the active substance is added and homogeneously dispersed therein with stirring. After the sugar, the sorbitol solution and the flavouring have been added and dissolved, the suspension is evacuated with stirring to eliminate air.

5 ml of suspension contain 50 mg of active substance.

Example 8

Ampoules containing 10 mg active substance

Composition:

active substance		10.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	2.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 2 ml ampoules.

Example 9

Ampoules containing 50 mg of active substance

Composition:

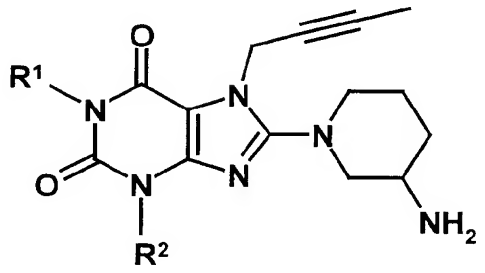
active substance		50.0 mg
0.01 N hydrochloric acid q.s.		
double-distilled water	ad	10.0 ml

Preparation:

The active substance is dissolved in the necessary amount of 0.01 N HCl, made isotonic with common salt, filtered sterile and transferred into 10 ml ampoules.

Patent Claims

1. Compounds of general formula



(I),

wherein

R^1 denotes a benzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-(trifluoromethyl)-benzyl, 3-(trifluoromethyl)-benzyl or 4-(trifluoromethyl)-benzyl group,

a 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-(difluoromethoxy)-benzyl, 3-(difluoromethoxy)-benzyl, 4-(difluoromethoxy)-benzyl, 2-(trifluoromethoxy)-benzyl, 3-(trifluoromethoxy)-benzyl or 4-(trifluoromethoxy)-benzyl group,

a 2-cyanobenzyl, 3-cyanobenzyl or 4-cyanobenzyl group,

a 2-cyano-3-methoxy-benzyl, 2-cyano-4-methoxy-benzyl, 2-cyano-5-methoxy-benzyl, 2-cyano-4-fluoro-benzyl, 2-cyano-5-fluoro-benzyl or 2-cyano-6-fluoro-benzyl group,

a 2-oxo-2-phenyl-ethyl or 2-(3-methoxy-phenyl)-2-oxo-ethyl group,

a 2-(3-methyl-2-oxo-2,3-dihydro-benzoxazol-4-yl)-2-oxo-ethyl group,

a (pyridin-2-yl)methyl, (3-cyanopyridin-2-yl)methyl, (6-cyanopyridin-2-yl)methyl, (5-cyano-pyridin-2-yl)methyl, (4-cyano-pyridin-2-yl)methyl, (4-cyano-pyridin-3-yl)methyl,

(3-cyano-pyridin-4-yl)methyl, (2-cyano-pyridin-3-yl)methyl, (2-cyano-pyridin-4-yl)methyl, (5-cyano-pyridin-3-yl)methyl or (6-cyano-pyridin-3-yl)methyl group,

a (3-cyano-quinolin-2-yl)methyl group,

a (1-cyano-isoquinolin-3-yl)methyl or (4-cyano-isoquinolin-1-yl)methyl group,

a (4-methyl-quinazolin-2-yl)methyl group,

a (quinoxalin-6-yl)methyl or (2,3-dimethyl-quinoxalin-6-yl)methyl group, or

a ([1,5]naphthyridin-2-yl)methyl group and

R^2 denotes a cyclopropyl or phenyl group,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

2. Compounds of general formula I according to claim 1, wherein

R^1 is defined as in claim 1 and R^2 denotes a cyclopropyl group,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

3. Compounds of general formula I according to claim 1, wherein

R^1 is defined as in claim 1 and R^2 denotes a phenyl group,

the tautomers, enantiomers, diastereomers, the mixtures thereof and the salts thereof.

4. Physiologically acceptable salts of the compounds according to at least one of claims 1 to 3 with inorganic or organic acids.

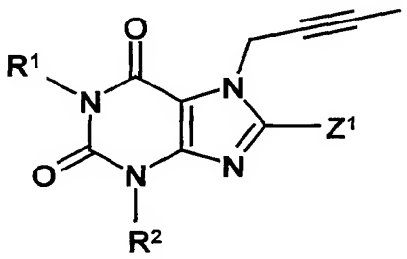
5. Pharmaceutical compositions, containing a compound according to at least one of claims 1 to 3 or a physiologically acceptable salt according to claim 4 optionally together with one or more inert carriers and/or diluents.

6. Use of a compound according to at least one of claims 1 to 4 for preparing a pharmaceutical composition which is suitable for the treatment of type I and type II diabetes mellitus, arthritis, obesity, allograft transplantation and osteoporosis caused by calcitonin.

7. Process for preparing a pharmaceutical composition according to claim 5, characterised in that a compound according to at least one of claims 1 to 4 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

8. Process for preparing the compounds of general formula I according to claims 1 to 4, characterised in that

a) a compound of general formula



(II),

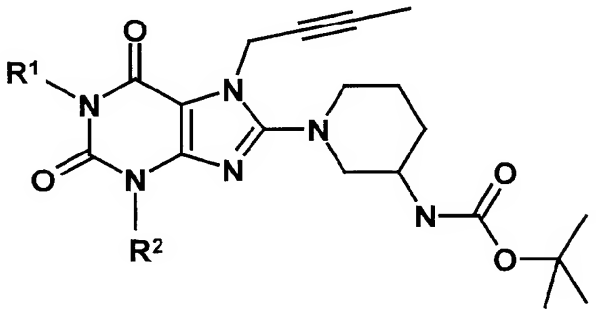
wherein

R^1 and R^2 are defined as in claims 1 to 3 and

Z^1 denotes a leaving group such as a halogen atom, a substituted hydroxy, mercapto, sulphinyl, sulphonyl or sulphonyloxy group,

is reacted with 3-aminopiperidine, the enantiomers or the salts thereof, or

b) a compound of general formula



(III),

wherein R^1 and R^2 are defined as in claims 1 to 3, is deprotected,

and/or

any protecting groups used during the reaction are then cleaved and/or

the compounds of general formula I thus obtained are resolved into their enantiomers and/or diastereomers and/or

the compounds of formula I thus obtained are converted into their salts, particularly for pharmaceutical use into the physiologically acceptable salts thereof with inorganic or organic acids.

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